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THE ENDOCRINOLOGIST

THE MAGAZINE OF THE SOCIETY FOR ENDOCRINOLOGY

What's new?
ADVANCES IN ENDOCRINOLOGY

Special features
PAGES 6–20

A word from THE EDITOR...

Welcome to the summer issue of *The Endocrinologist*! Our theme is 'What's new?', as we bring together emerging developments in the worlds of endocrinology and wider discovery bioscience.

As technology evolves, so does its implementation for patient care. This is exemplified by the recent advancements in management of type 1 diabetes (page 6). In keeping with our theme, this issue also outlines progress in obesity management (page 7) and thyroid disease (page 10), with a concise summary of recent updates to the NICE guideline for the management of thyroid disease.

On page 12, you can learn about the emerging role of specialist pharmacists in endocrinology, with three case studies on the application and utility of these posts. The first of our updates on neuroendocrine tumours (NETs) is a tour de force on functional pituitary adenoma imaging (page 14). The second brings us up to date on the utility of single cell RNA sequencing to understand specific NET signatures for therapeutic design/targeting, and the role of laboratory models for novel drug design (page 16). Two articles by members of *The Endocrinologist*'s Editorial Board provide a timely update on how COVID-19 infection affects endocrine organs (page 9), and debunk 'exerkines', the new secretory factors on the block (page 18).

I very much enjoyed the opportunity to interview the Society for Endocrinology 2022 Starling Medal recipient, Cynthia Andoniadou (see page 19). We discussed her programmes of research in endocrine stem cells, and she gave a low down on the pros and cons of the multi-omics approaches they have used to explore how intercellular signals modulate cell fate and function. We complete this issue with an obituary for Professor David Baird on page 30; he was an absolute pioneer in reproductive endocrinology, as his colleagues and friends recall.

I encourage you to submit your nominations for the Society for Endocrinology Medals 2023, and the Outstanding Clinical Practitioner and Teaching Achievement Awards, by 4 July (page 26). This is our opportunity to celebrate achievements in endocrine research, clinical practice and the education of our field's future leaders.

As always, we hope you enjoy reading this issue; it has been fun to put it together. I wish you a productive yet restful summer, hopefully with some sunshine!

KIM JONAS

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NEW FOR YOU
Opportunities from your Society

Become a contributor... Contact the Editorial office at **endocrinologist@endocrinology.org**

The Society welcomes news items, contributions, article suggestions and letters to the Editor. We would also like to hear your feedback on this issue of the magazine.

Deadline for news items for the AUTUMN 2022 issue: **1 July 2022**.

Front cover image ©Shutterstock

SOCIETY SUPPORT FOR YOUR ENDOCRINE EVENTS

You can apply for up to £10,000 to help fund the organisation of your own event. Whatever you're planning, whether it's small or large, or has a clinical, nursing or scientific focus, we welcome your applications for our Meeting Support Grant. Check the listings in the calendar of Society-supported events (right) to see the meetings that are already benefiting from this grant. We will also help you promote it to our members – and beyond! The next deadline is 23 November 2022. Find out more at **www.endocrinology.org/grants-and-awards**.

ONLINE TRAINING OPPORTUNITIES

Our SfE Skills Academy is back for 2022. Our educational webinar series for clinicians, endocrine nurses and researchers is kicking off on 7 July with a Clinical Skills Webinar. Join Aled Rees and Richard Quinton for a session on PCOS & Hyperandrogenism.

Learn more and register at **www.endocrinology.org/clinical-skills-webinars-2022**.

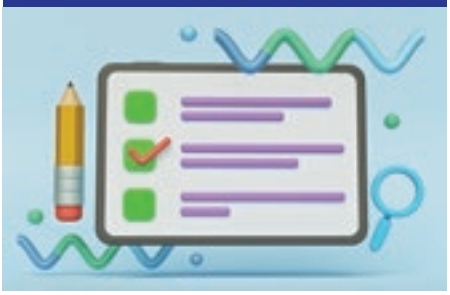
INSPIRE THE NEXT GENERATION

Apply for a Public Engagement Grant to create learning resources for our website 'You and YourHormones' or to help school teachers and pupils learn about endocrinology. Funding is available for worksheets, factsheets or quizzes, short videos or podcasts, or anything else you can think of. Apply by 21 September. Visit **www.endocrinology.org/public-engagement-grant** to find out more.

SHARE YOUR AUDITS, SURVEYS AND RESEARCH PROJECTS WITH THE ENDOCRINE COMMUNITY

Advance your own work, as well as wider endocrine research and clinical practice by getting input from other members for your audits and surveys.

Go to **www.endocrinology.org/sharemywork** to submit yours and to contribute to current projects.



SHARE YOUR WORK AT SfE BES 2022

Don't miss the SfE BES abstract deadline on **27 June 2022**! Submit your work at **www.endocrinology.org/sfebes2022**. If you are an Early Career Member, you can also apply for one of our Prize Lectures. Not only will you have the opportunity to present at SfE BES 2022, you will also receive an honorarium and write an article for *The Endocrinologist*. Learn more about our Early Career Prize Lectures at **www.endocrinology.org/ecpl**.

APPLY FOR A ROLE WITHIN YOUR SOCIETY

Help shape the future of your Society by applying for one of our Council, Committee or Endocrine Network Convenor vacancies. This is your opportunity to have your say and represent our diverse membership. Apply by **5 September 2022**. Learn more at **www.endocrinology.org/represent**.

ARE YOU MAKING THE MOST OF YOUR MEMBERSHIP?

As a member of the Society for Endocrinology, you will be supported at every stage of your career and be introduced to a network of colleagues that share your passion. Our range of member benefits are now even easier to review and tailored for each member category, including our Associated Professional members. Find out more at **www.endocrinology.org/memberbenefits**.

ADVERTISE YOUR JOBS TO OVER 3,000 ENDOCRINOLOGISTS

We can highlight your job vacancies to members, and help you to attract the best candidates from the endocrine community. Email your job adverts to **media@endocrinology.org** and view current vacancies at **www.endocrinology.org/careers/jobs**.

SOCIETY CALENDAR

7 July 2022
CLINICAL SKILLS WEBINAR
Online

14–16 November 2022
SfE BES 2022
Harrogate, UK

www.endocrinology.org/events for full details

SOCIETY-SUPPORTED EVENTS

5 July 2022
PHYSICAL ACTIVITY AND THE ENDOCRINE SYSTEM
Nottingham, UK

16–17 July 2022
EARLY CAREER PHYSICIANS AND INVESTIGATORS CONFERENCE
Birmingham, UK

15 September 2022
ENERGY STRESS MEETING
Liverpool, UK

SOCIETY-ENDORSED EVENTS

22–23 September 2022
OXFORD ENDOCRINOLOGY MASTERCLASS 2022
Oxford, UK

SOCIETY DEADLINES

27 June 2022
SfE BES ABSTRACT SUBMISSION

4 July 2022
EARLY CAREER PRIZE LECTURE

4 July 2022
MEDAL NOMINATIONS

4 July 2022
OUTSTANDING CLINICAL PRACTITIONER AWARD

4 July 2022
TEACHING ACHIEVEMENT AWARD

10 August 2022
TRAVEL GRANT

5 September 2022
COUNCIL, COMMITTEE & ENDOCRINE NETWORK CONVENOR APPLICATIONS

21 September 2022
PUBLIC ENGAGEMENT GRANT

23 November 2022
MEETING SUPPORT GRANT

www.endocrinology.org/grants for full details of all Society grants and prizes

HOT TOPICS

SOCIETY FOR ENDOCRINOLOGY OFFICIAL JOURNALS

Society members have free access to the current content of *Journal of Endocrinology*, *Journal of Molecular Endocrinology*, *Endocrine-Related Cancer* and *Clinical Endocrinology* via the Members' Area on the Society website, **www.endocrinology.org**. *Endocrine Connections*, *Endocrinology, Diabetes & Metabolism Case Reports* and *Endocrine Oncology* are open access and free to all. Publishing in *Endocrine Oncology* is currently free.

JOURNAL OF ENDOCRINOLOGY

Pesticide-induced endocrine disruption of the bovine cervix

The impact of pesticides on our health and well-being has become increasingly important over recent decades, given their roles in food production and around the home. The most commonly used type are the pyrethroids, which are also a huge health concern for aquatic life.

Wrobel *et al.* have now investigated the role these pesticides may have in endocrinology, for the first time. Utilising cervical cells from cows during the periovulation period, the group tested two insecticides, cypermethrin and fenvalerate, at a range of concentrations. They found that fenvalerate has the potential to induce endocrine disruption of the cervix.

Despite being a very early study, it is nevertheless incredibly interesting and has the potential to affect our understanding of and interactions with these pesticides.

Read the full article in *Journal of Endocrinology* **253** 133–142

JOURNAL OF MOLECULAR ENDOCRINOLOGY

Models of ERα deletion examine oestrogen's role in obesity

Oestrogen has long been implicated in how we manage our weight, and is often seen to be protective against obesity. However, our understanding of this sex hormone's direct role is lacking.

Saavedra-Peña *et al.* have shown that a deletion in oestrogen receptor-α (ERα) from adipocytes does not affect adipose or fat mass in male or female mice. This is regardless of diet. What is interesting, however, is that loss of this receptor in early precursor cells does lead to exacerbated obesity when on a high fat diet.

This study illustrates the intricacies and difficulties in studying hormones in model animals, and should be explored for the authors' robust attempt at solving a long-held mystery.

Read the full article in *Journal of Molecular Endocrinology* **68** 179–194

ENDOCRINE-RELATED CANCER

Clinical implications of thyroid cancer's immune microenvironment

This review article by Cunha & Ward attempts to collate the current knowledge of the immune microenvironment relating to thyroid cancer, with specific relevance to those in clinical practice.

Thyroid cancer, in particular, is a shining example of why the immune system needs to be examined more closely, as it often presents with localised immune responses. Here, we are introduced to a complex cross-talk between cells from the immune and endocrine systems, suggesting numerous new avenues for therapeutic approaches to thyroid cancer treatment.

With a stark reminder that up to 30% of thyroid cancer cases move down unfavourable pathways during treatment, this review sheds light on new immunotherapies, with an eye on both preclinical and clinical settings, to help patients for years to come.

Read the full article in *Endocrine-Related Cancer* **29** R67–R83

CLINICAL ENDOCRINOLOGY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What can endocrine patients learn from elite athletes?

Exercise-related medicine is throwing open many opportunities for further research, and developing our understanding of the human body. Amongst these, the endocrine aspects of various forms of exercise are being studied.

In this article, McCarthy *et al.* provide an overview of what is currently known and what additional research is ongoing, while raising further questions along the way. They also provide some interesting information regarding exercise in younger people, and variations with increasing age.

The review examines research evidence regarding endocrine changes in high-performing athletes, with relevance to encouraging patients to exercise safely. It discusses the adaptability of human endocrine-metabolic-physiological systems and the value of understanding maladaptation to physical training and nutrition, especially in the young. The authors also consider the use of physical activity in some endocrine conditions.

Read the full article in *Clinical Endocrinology* **96** 781–792

Hot Topics is written by Sophie Clarke, Craig Doig, Louise Hunter, Gareth Nye and Venkatram Subramanian.

ENDOCRINE CONNECTIONS

Antenatal thyroid hormone and antithyroid therapy: 2004–2018

Thyroid hormones play critical roles in fetal development and maternal health. Thyroid dysfunction can manifest in healthy women during pregnancy and be difficult to diagnose. However, despite increasing awareness of thyroid disease during pregnancy, rates of incidence and geographical patterns remain unclear.

Bakken *et al.* examined both the Medical Birth Registry of Norway and the Norwegian Prescription Database over a 14-year period (a total of 855,067 pregnancies). From these data cohorts, they revealed that use of thyroid replacement therapy increased from 1.45% in 2004 to 3.57% in 2018. Use of antithyroid therapy was lower, but increased more than twofold (0.10%) during this period.

This study highlights the value of historical patient datasets, as well as evidencing the increases in awareness of thyroid dysfunction during pregnancy.

Read the full article in *Endocrine Connections* **11** e210631

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ENDOCRINOLOGY, DIABETES & METABOLISM CASE REPORTS

Oral levothyroxine in initial treatment of myxoedema coma

Chamba and colleagues, working in Tanzania, describe the effective use of high dose oral levothyroxine to treat profound hypothyroidism. They report the case of a 67-year-old woman who had undergone total thyroidectomy for multinodular goitre, who was prescribed levothyroxine (100µg daily) for thyroid replacement.

After 3 years, she presented with breathlessness, weight gain, constipation and cold intolerance. Clinical examination revealed hypothermia and signs of congestive cardiac failure. Investigations demonstrated hyponatraemia, hypocalcaemia and an elevated partial thromboplastin time. Left ventricle dilatation was evident on echocardiogram, and electrocardiogram showed low voltage activity and a prolonged QT interval. The course of hospital admission was complicated by spontaneous bleeding (haematuria, ecchymosis), and a reduced level of consciousness. A review of thyroid biochemistry demonstrated elevated levels of thyroid-stimulating hormone for at least 1 year preceding admission, and markedly low free thyroid hormone levels at presentation.

The team initiated oral levothyroxine (300µg daily), intravenous hydrocortisone and oral calcium, plus supportive treatment for heart failure and hypothermia. Over the following 3 weeks, the patient made a gradual recovery, and was euthyroid at follow-up 3 months later.

In summarising her case, the team discuss the features of severe hypothyroidism (myxoedema coma), and the use of levothyroxine and liothyronine in its management.

Read the full article in *Endocrinology, Diabetes & Metabolism Case Reports* doi:10.1530/EDM-21-0197

ENDOCRINE HIGHLIGHTS

A summary of papers from around the endocrine community that have got you talking.

Reversible phosphorylation stabilises tRNA for thermotolerance

Post-translational modification is a fundamental mechanism used to regulate the biological activity of proteins. As such, the addition or removal of phosphate groups from amino acids is one of the most studied and well understood of all post-translational modifications.

Ohira *et al.* reveal an additional layer of control in the process of ribosomal translation, with identification of reversible phosphorylation of the fundamental transfer RNA (tRNA) molecule. This work shows that phosphorylation of tRNA modulates its capacity to perform the critical process of translation. They also show this is not a process that changes the translated sequence, only the rate at which it is produced.

This has important ramifications for our understanding of how cells respond to the assortment of stressors that exist, including oxygen concentration, nutrients and redox status.

Read the full article in *Nature* **605** 372–379

Calorie restriction with or without time-restricted eating in weight loss

Time-restricted eating has emerged as a potential strategy to achieve weight loss in subjects with obesity. It describes a practice of intermittent fasting, whereby the hours within which an individual can eat are limited across 24 hours. In some small pilot studies, time- restricted eating was associated with reduced fat mass and body weight in patients with obesity, but these studies were not adequate to support changes to clinical guidelines.

In this randomised, controlled trial, conducted in China, Liu *et al.* instructed 139 participants aged 18–75 (body mass index 28–45kg/m^2) to follow a calorie-restricted diet, either in a time-restricted window (08.00 to 16.00) or at times chosen by the individual participants. At 12 months of follow-up, 118 participants remained. The percentage weight loss from baseline was 9.0% (8kg) in the time-restriction group, and 7.2% (6.3kg) in the calorie-restriction-only group (group difference –1.8kg, P=0.11). There was no difference between the groups in blood pressure, waist circumference or other markers of metabolic health, such as lipid levels.

The study is limited by its relatively small sample size, and by the fact that the period for eating at baseline was shorter than has been reported elsewhere (so the change incurred by restricting eating to 08.00–16.00 may not have been very great). However, the authors suggest that time-restricted eating may be a useful approach to accomplish calorie restriction without the resources required for traditional models of intentional restriction of calories. Further research is warranted to determine the generalisability of these findings.

Read the full article in *New England Journal of Medicine* **386** 1495–1504

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THE CHANGING LANDSCAPE OF TECHNOLOGY IN TYPE 1 DIABETES

WRITTEN BY REZA ZAIDI, FULYA MEHTA AND PARTHA KAR

In the quest to improve glycaemic management, advances in wearable technology have transformed care for people with type 1 diabetes (PWD) and healthcare professionals (HCPs). The management of type 1 diabetes intrinsically involves regular glucose monitoring, appropriate insulin dosing and balancing the burden of hypo- and hyperglycaemia, with an eventual aim of reducing the risk of long term complications. Interpretation of the data generated has offered new perspectives to PWD and HCPs in management of the disease and making therapeutic decisions.

Healthcare policy and clinical guidance have aligned with contemporary research outcomes to allow wider and regular uptake of technology for type 1 diabetes care in the NHS. Outcomes thus far have shown significant improvements in glycaemic markers, hospitalisation rates and quality of life across the age spectrum.

CLOSED LOOP SYSTEMS: THE 'NEW KID ON THE BLOCK'

Continuous glucose monitoring (CGM) is of two types: real time (rtCGM) or intermittently scanned (isCGM). rtCGM systems (Dexcom, Medtronic, Medtrum) measure glucose every few minutes and actively transmit data wirelessly from the sensor to a reader or smartphone app, whereas isCGM systems (FreeStyle Libre) transmit data only when the user scans their sensor with a reader or smartphone app.

The development of closed loop systems, which link rtCGM to various insulin pumps and automatically adjust insulin delivery via an algorithm, have revolutionised the management of type 1 diabetes in patients. Four hybrid closed loop systems are currently available and licensed for use in PWD, with various minimum ages for use. These systems are: the 670G hybrid closed loop (HCL) system and 780G advanced HCL (Medtronic, Northridge, CA, USA), the CamAPS FX interoperable app (CamDiab, Cambridge, UK), and the Control IQ system (Tandem Inc., San Diego, CA, USA). Clinical trials show that hybrid closed loop insulin delivery is safe and improves glycaemic outcomes in PWD.

Closed loop systems have revolutionised the management of type 1 diabetes in patients.. ©Shutterstock

TIME IN RANGE: MOVING ON FROM HbA1c

Glycated haemoglobin (HbA1c) has been a widely available measure of glycaemic management and considered a 'gold standard' in assessing the risk of complications. Amongst the many limitations, it does not give an accurate indication of day-to-day variability of glucose levels, which effects the overall well-being of PWD.

'Healthcare policy and clinical guidance have aligned with contemporary research outcomes to allow wider and regular uptake of technology for type 1 diabetes care in the NHS.'

A plethora of data are generated from rtCGM and isCGM for standardised analysis, endorsed by international consensus, which gives highly valuable information. Amongst them, the proportion of the time a PWD spends each day in a defined target range constitutes the concept of 'time in range' or %TIR (3.9–10.0mmol/l). This measure is responsive to changes in diet and aspects of lifestyle, to aid in therapeutic decision making for PWD and HCPs.

In addition, the International Consensus on Time in Range has defined clear targets for PWD, women with type 1 diabetes in pregnancy, older individuals and those with hypoglycaemia unawareness. Furthermore, extrapolation of data from 1440 Diabetes Control and Complications Trial participants and reanalysis has shown a 40% reduction in microalbuminuria and a 64% reduction in retinopathy for every 10% increase in %TIR.

CHALLENGES IN TECHNOLOGY UPTAKE

In recent years, there has been encouraging progress in the uptake of technology in the UK. This has been boosted by the national rollout of FreeStyle Libre, successful procurement of all commercially available insulin pump systems and changes to NICE guidance on CGM for type 1 diabetes in pregnancy, resulting in a third of individuals with type 1 diabetes using CGM.

Within this progress lies obvious challenges. Similar to trends in healthcare access, uptake of technology in type 1 diabetes also witnesses inequalities amongst different populations and indices of socioeconomic deprivation. A conspicuous drop in usage during adolescence and young adulthood due to alarm burnout and peer pressure, amongst other factors, adds further challenges during transition from paediatric to adult diabetes care.

Additionally, regional organisational and service delivery barriers can further restrict the widespread use in an eligible population.

WHAT THE FUTURE HOLDS

The landscape of technology in type 1 diabetes care is changing at an unprecedented pace. More sophisticated commercial systems are being developed by industry and being rolled out early as a result of the success seen in recent years.

Radical changes to the NICE eligibility criteria in 2022 will result in wider availability of CGM to all individuals with type 1 diabetes. The ongoing real world HCL trial in England will further shed light on its effectiveness across children, young people and adults, with results expected towards the end of 2022.

FURTHER READING

1. Wilmot EG *et al.* 2021 *Diabetic Medicine* **38** e14433.
2. Battelino T *et al.* 2019 *Diabetes Care* **42** 1593–1603.
3. Messer LH *et al.* 2019 *Diabetes Technology & Therapeutics* **21** 462–469.
4. Ng SM & Evans ML 2021 *Diabetic Medicine* **38** e14620.

The aim to reduce inequalities in uptake remains at the forefront of current policy and transformational plans within NHS England. However, individualised care, support and education, with clinical leadership, remain the most powerful drivers, as always, in adoption of 'game-changing' technology within type 1 diabetes care in the NHS.

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A NEW ERA IN OBESITY MANAGEMENT

WRITTEN BY AKHEEL SYED

Obesity is not a new phenomenon, it's as old as humanity itself. The Venus of Willendorf (Vienna, Austria) stands testimony to the recognition, and perhaps celebration, of (pathological) voluptuousness in the Palaeolithic era (pictured on page 8).

What is new, however, is the unimaginable scale of the obesity epidemic today. The World Health Organization estimates that, as of 2016, over 650 million adults (13%) globally had clinical obesity. The situation is worse in Western countries: 28% of adults in England and 42% in the USA have obesity.

HOW DID WE GET HERE?

It's complicated! The situation is the result of a perfect storm of evolutionary biology adapted for energy conservation, honed by genetic selection through millennia of food insecurity, laid low by the fruits of the industrial revolution.

A dawning realisation of the strong biological underpinnings of obesity as a 'disease', not a 'lack of moral fibre' (as has often been stigmatisingly made out in popular culture), has come from advances in our understanding of genetic and epigenetic influences, the interplay of complex endocrine pathways, the gut microbiome, and our interaction with the built environment. The Foresight report, *Tackling Obesities*, identified a huge range of factors that influence obesity in broad clusters of physiology, individual psychology, individual activity, physical environment, societal influences, food production and food consumption.[1]

HISTORICAL MANAGEMENT

In the face of such complexity, the management of obesity has often been an overly simplistic 'a calorie in, a calorie out' mantra. Galen of Pergamon, sharing his tips two millennia ago, declared, "I reduced a huge fat fellow to a moderate size in a short time, by making him run every morning until he fell into a profuse sweat; I then had him rubbed hard, and put into a warm bath; after which I ordered him a small breakfast, and sent him to the warm bath a second time. Some hours after, I permitted him to eat freely of food, which afforded but little nourishment; and lastly, set him to some work which he was accustomed to for the remaining part of the day."

So, how far have we come since Galen? The DiRECT study has shown the efficacy of lifestyle and dietary changes for weight loss and diabetes remission for up to two years in people with type 2 diabetes.[2] However, the success of non-drug weight management on a long term epidemiological scale is rarely lasting.

The pursuit of effective adjunctive weight loss medications has come a long way since DNP (2,4-dinitrophenol) in the 1930s, which induced

'Whilst many more agents are on the horizon, the holy grail of a single common target for the treatment of "idiopathic" obesity may instead prove to be a multilevel, multichannel product incorporating several molecules.'

thermogenesis by uncoupling of oxidative phosphorylation – literally a 'fat burner' that caused death by hyperthermia! The past couple of decades have seen the marketing and subsequent withdrawal of weight loss products such as rimonabant (psychiatric adverse effects) and sibutramine (cardiovascular events). Thus, orlistat was the only licensed medicinal product for weight loss in the UK/EU for much of the 2010s.

THE DAWN OF A NEW ERA

It is now the dawn of a new era of medical therapies for obesity. Many have cut their proverbial teeth in the treatment of type 2 diabetes. Whilst all agents from the glucagon-like peptide 1 (GLP1) receptor agonist class have proved their weight loss benefits, two products – liraglutide and semaglutide – now have marketing authorisation for a weight loss indication.

From the early days of recombinant leptin therapy in congenital leptin deficiency,[3] targeted drug discovery for single gene disorders has brought the promise of effective weight loss therapy for pro-opiomelanocortin, proprotein subtilisin/kexin type 1 and leptin receptor deficiency syndromes, with the first-in-class melanocortin-4 receptor agonist setmelanotide[4–6] approved for use in 2020–2021.

Whilst many more agents are on the horizon, the holy grail of a single common target for the treatment of 'idiopathic' obesity may instead prove to be a multilevel, multichannel product incorporating several molecules. We are already seeing that with some novel products in development, such as GLP1–glucagon, glucose-dependent insulinotropic polypeptide (GIP)–GLP1 and amylin–calcitonin dual agonists, and GIP–GLP1–glucagon tri-agonists.[7] Some are approaching an efficacy similar to that of bariatric surgery.

SURGICAL APPROACHES

Bariatric surgery itself has come a long way since the 10th century when, it is claimed, King Sancho I of León (Spain), nicknamed Sancho the Fat, underwent suturing of his lips to restrict him to a liquid diet through a straw. He is said to have lost half his weight, to return triumphant to regain his throne.[8]

Bariatric surgery has rapidly evolved from the jejuno–ileal bypass of the 1950s to modern day laparoscopic techniques. Whilst minimally invasive endoscopic techniques are continually being developed, sleeve gastrectomy and gastric bypass have stood the test of time for weight reduction, remission or amelioration of weight-related co-morbidities, and improvement in life expectancy,[9] earning the epithet 'metabolic surgery'. It didn't take long for bariatric surgeons to troll diabetologists with the assertion, "Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus."[10]

An exciting fallout from bariatric surgery is its effect on cancer risk. Cancer Research UK's adverts of a few years ago, highlighting that obesity has overtaken smoking as the leading cause of bowel, kidney, ovarian and liver cancers, may have been derided as scaremongering. However, the significantly increased risk of several cancers in people with obesity is undeniable.

Endometrial cancer is a case in point. The fourth most common cancer of women in the UK, its risk is increased by 50% for every 5kg/m^2 excess body mass index. Our group has shown that significant weight loss (by bariatric surgery or lifestyle and dietary management) can reverse endometrial precancerous changes.[11,12]

Similarly, the risks of obesity and the benefits of weight loss are increasingly recognised in women with infertility and patients awaiting organ transplantation. We now have local pathways for intensive weight management and/or expedited bariatric surgery for such patients.

Venus of Willendorf, a female Palaeolithic limestone figurine tinted with red ochre. ©Naturhistorisches Museum, Vienna/Steven Zucker (reproduced under CC BY-NC-SA 2.0 licence; https://creativecommons.org/licenses/by-nc-sa/2.0)

We are on the cusp of a revolution in medical therapies for obesity, but cost-effectiveness remains a hindrance until drug pricing becomes affordable. Until such time, bariatric surgery remains the most clinically effective and cost-effective treatment there is for severe obesity.[13]

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NEW UNDERSTANDING OF THE ENDOCRINE EFFECTS OF COVID-19

WRITTEN BY SOPHIE CLARKE

The effects of the COVID-19 pandemic continue to be felt throughout healthcare systems around the world. Although efforts remain focused on managing the acute effects of the infection, long COVID is increasingly recognised as a complication of even mild infection with SARS-CoV-2.

Estimates suggest that 1.5 million people in the UK have experienced symptoms of COVID beyond 4 weeks after initial infection. Of these, 71% have experienced symptoms for at least 12 weeks.[1] Fatigue is most frequently reported, alongside hair loss, reduced libido, menstrual irregularity and palpitations, and so there is considerable overlap with symptoms of endocrine dysfunction. The endocrine system is vulnerable to disruption by COVID-19, both due to the nature of the precise vascular supply to endocrine glands, and because several endocrine glands possess the receptor (ACE2) and protein (TMPRSS2) needed for the SARS-CoV-2 virus to access cells.

THYROID EFFECTS

One of the more frequently encountered changes to endocrine function in patients with acute COVID-19 is thyroid dysfunction. Non-thyroidal illness (NTI), characterised by global reductions in thyrotrophin (TSH), free tri-iodothyronine (fT3) and free thyroxine (fT4), affects up to 7% of patients with mild–moderate acute COVID-19.[2] It occurs due to a reduction in hypothalamic TSH-releasing hormone and is observed at times of physiological stress.

In a smaller proportion of patients, subacute thyroiditis and autoimmune thyroid dysfunction (Graves' disease) have also been observed in cases of COVID-19. However, there is currently no evidence demonstrating persistent thyroid dysfunction in patients with long COVID. Indeed, in patients at 12 weeks' follow up, thyroid function was not different in those with fatigue compared with those without.[3]

ADRENAL FUNCTION

Recently, histopathological evidence of adrenal gland destruction has been presented from patients who died from COVID-19. One group observed adrenal inflammation, widespread microthrombosis and reduction of cortisone intensities,[4] whilst another demonstrated the SARS-CoV-2 spike protein in adrenocortical cells, as well as SARS-CoV-2 mRNA.[5] Case reports of adrenal haemorrhage and adrenal infarction have also been reported in patients presenting with adrenal insufficiency after COVID-19.

Yet, current evidence suggests that, for the majority of patients, adrenal function is preserved after COVID-19 infection. We observed a normal cortisol response following administration of Synacthen (tetracosactide) to patients who survived COVID-19, even in those with persistent fatigue 12 weeks after initial infection.[3] Additionally, although a minority had dehydroepiandrosterone sulphate (DHEAS) values below the age and sex reference range, DHEAS was not different in those who were tired, compared with those who were not, further reflecting preserved adrenal function in patients who survive COVID-19.[6] Whilst national data are yet to be collated, this confirms clinical experience; we are not encountering the significant numbers of patients with adrenal insufficiency that we might expect, were adrenal damage a frequent complication of COVID-19.

REPRODUCTIVE IMPACT

The reproductive system is inherently vulnerable to disruption by systemic illness. There has been focus on the impact of COVID-19 on the hypothalamic–pituitary–gonadal axis. Ovarian ACE2 mRNA has been detected in both pre- and post-menopausal women, as well as in the endometrium. Furthermore, ACE2 regulates angiotensin, which helps facilitate regulation of oocyte maturation and corpus luteum maintenance.

Patients with mild COVID-19 reported prolonged cycle length, and serum anti-müllerian hormone levels were lower in patients with COVID-19, compared with controls.[7] However, there are multiple factors that may contribute to disruption of the hypothalamic–pituitary–gonadal axis, including psychological stress – a significant factor for many individuals during the pandemic. To date, however, there is no evidence that COVID-19 results in persistent perturbation of menstrual regularity.

The male reproductive tract possesses ACE2 receptors, specifically in the Leydig and Sertoli cells.[8] Additionally, patients with COVID-19 have been observed to have both acute and subacute orchitis. In a seven-month follow-up study of 121 patients, total testosterone was observed to increase significantly compared with baseline on admission, although, interestingly, 55% of patients were hypogonadal. However, total testosterone at seven months' follow up was associated with co-morbidities, suggesting that factors other than COVID-19 were influencing testosterone values at this time.[9]

METABOLIC EFFECTS

Finally, perhaps one of the most frequent endocrine disturbances experienced during the pandemic is that of hyperglycaemia and ketosis, even in patients not known to be diabetic. SARS-CoV-2 viral mRNA has been detected in the β cells of patients with COVID-19 at autopsy, and autoantibody-negative type 1 diabetes and insulinopenia have been reported acutely in patients with COVID-19. Additionally, at six months after admission, more than a third of patients who were observed to have hyperglycaemia during their acute admission had persistent hyperglycaemia and ~2% had new-onset diabetes.[10] However, in our cohort, C peptide values were preserved at three months of follow up,[11] and others have shown that it is significant insulin resistance that predominantly contributes to the insulin insufficiency observed.[12]

IN SUMMARY

The endocrine system is vulnerable to disruption by the SARS-CoV-2 virus. Whilst the focus is now shifting from the effects of acute infection to prolonged and persistent effects, there remains little evidence to suggest that endocrine disruption contributes to the syndrome of long COVID, although large scale studies remain to be undertaken.

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THE LATEST GUIDANCE IN MANAGING THYROID DISEASE

WRITTEN BY VENKATRAM SUBRAMANIAN

Thyroid disorders are one of the most common causes for referral to the endocrinology outpatient clinic. This process has been managed using guidelines which are regularly updated. The main points of reference for decisions regarding the management of thyroid disease are NICE Clinical Knowledge Summaries and resources provided by the British Thyroid Association, the European Thyroid Association and the American Thyroid Association. These usefully guide the clinician in decisions regarding treatment, which can then be further tailored to a patient's clinical presentation.

NICE Guideline 145 is the UK's most recently updated compendium, including treatment for patients with either hyperthyroidism or hypothyroidism, using evidence from most recent research studies and clinical trials.

Management can vary depending on the age of the individual affected. There are variations for pregnancy and childhood, as well as acceptance of conservative approaches in situations where more radical therapy may prove counter-productive or potentially adversely affect the quality of life of the individual concerned.

Rather than going through each individual guideline, the focus here will be to try and provide a concise summary of the various guidelines in their latest iterations. There were some disruptions to normal service due to COVID, but these have now started to normalise.

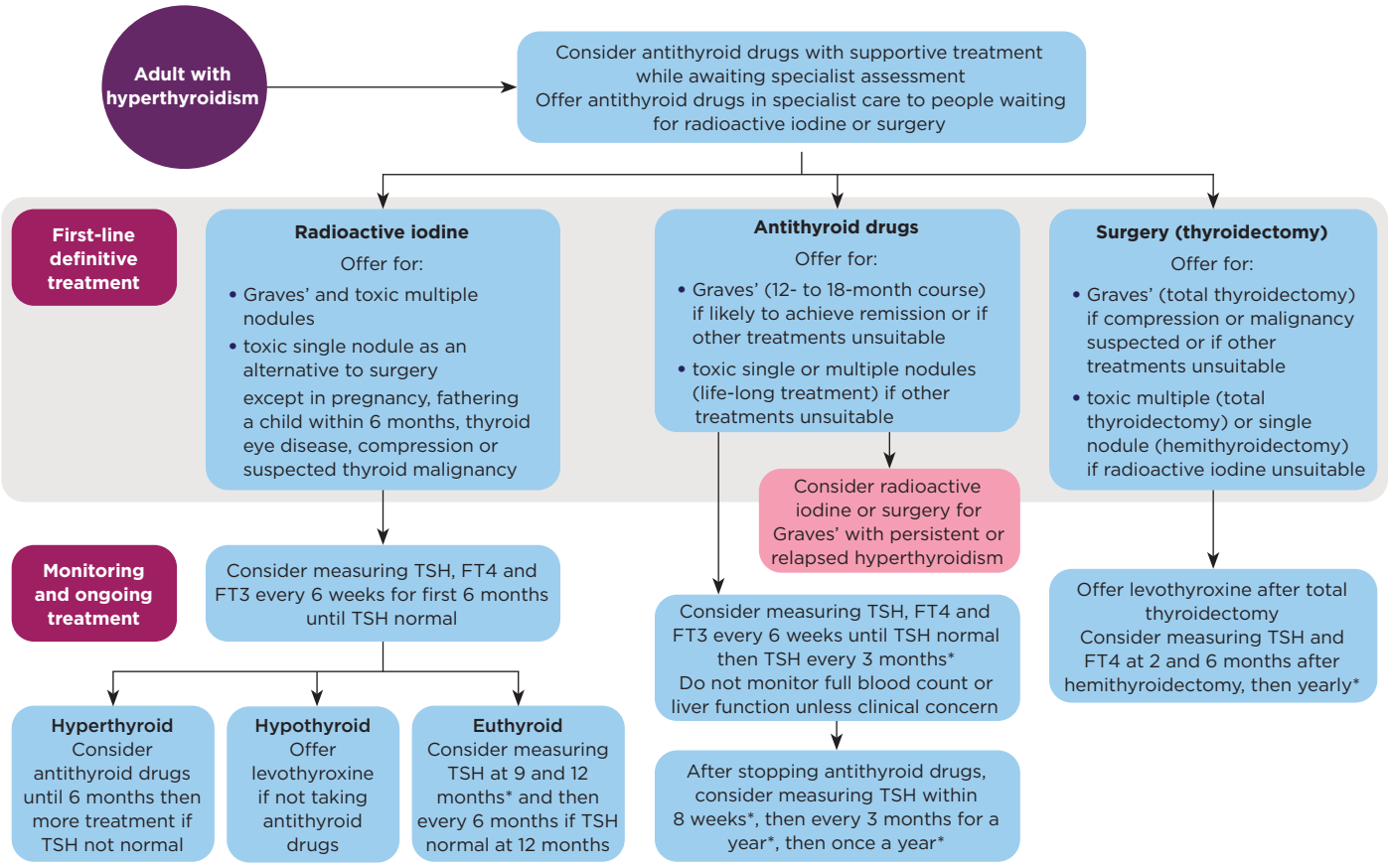
HYPERTHYROIDISM

Hyperthyroidism is mostly managed in secondary care by endocrinologists and endocrine specialist nurses with an interest in thyroid disease.

Initial investigations and management should involve taking a good history and identification or ruling out of the presence of thyroid eye disease and any other systemic effects of thyroid hormone excess.

Antithyroid hormone medications, such as propylthiouracil and methimazole/carbimazole, can be commenced in the first instance.

Hyperthyroidism in adults: management and monitoring. FT3, free tri-iodothyronine; FT4, free thyroxine; TSH, thyrotrophin. *With cascading – measuring FT4 in the same sample if TSH is above the reference range, and FT4 and FT3 in the same sample if TSH is below the reference range.



Thyrotrophin receptor antibodies are an important diagnostic tool in differentiating between autoimmune thyrotoxicosis and transient hyperthyroidism, which can occur in post-viral situations or in the early inflammatory stages of autoimmune hypothyroidism.[1]

In a departure from the previous approach, NICE recommends discussing the use of radioactive iodine (RAI) with patients during the first consultation. The indications for RAI are Graves' disease and toxic multiple nodules or toxic single nodule, as an alternative to surgery; the exceptions are cases of pregnancy, fathering a child within 6 months, thyroid eye disease, compression or suspected thyroid malignancy. Otherwise, the recommendation remains for 12–18 months of antithyroid drugs, but leaving the door open for RAI or surgery in the event of hyperthyroidism which is difficult to control.[2]

Surgery should also be discussed in the event of any evidence of compression on local structures or suspected/confirmed malignancy.

NICE has provided a summary sheet for quick guidance on management. This includes monitoring post-RAI or surgical definitive treatment (see Figure).

There have also been updates to the recommended periods of observation for monitoring and treatment of subclinical hyperthyroidism. Such patients may be discharged if their levels remain stable, with no evidence of cardiovascular/metabolic pathologies after six months or two subsequent stable levels. When in doubt, it is advised to recheck the levels using a different laboratory, to ensure standardisation of reporting and rule out assay interference.

The European Group on Graves' Orbitopathy has recently published updated guidelines for the management of thyroid orbitopathy. The focus is on ensuring a multidisciplinary team approach and use of pulse intravenous methylprednisolone. Other second-line treatments that are advised include a combination of oral steroids with azathioprine or cyclosporine, teprotumumab, tocilizumab or rituximab. These will all need a specialised approach. In mild cases, the use of selenium is recommended for patients in selenium-deficient regions. These treatments may need to be combined with local steroid injections and/or orbital radiotherapy. RAI is to be used in caution in Graves' orbitopathy.[3]

HYPOTHYROIDISM

Treatment and management of hypothyroidism have predominantly migrated to the remit of primary care, with secondary care involvement only in certain scenarios.

The cut-off for a raised thyrotrophin at which treatment is recommended has been established at ≥10mIU/l on two separate occasions three months apart.

The recommended starting dose for levothyroxine, as per NICE, is 1.6µg/kg in the absence of cardiovascular disorders, and needs to be adjusted to the nearest 25µg dose for dispensing purposes.

NICE recommends not using liothyronine or natural thyroid hormone extracts in the treatment of hypothyroidism. This statement has naturally sparked debate, but the recommendation is based on current available clinical research, which does not support the use of these medications.

However, as per the European Thyroid Association guidelines, a supervised trial may be considered after careful discussions with patients about expectations, with a clearly defined time frame to monitor for any response. The recommendation also states that this could be considered in patients who have hypothyroidism and have not had symptomatic relief, despite optimal attempts with standard levothyroxine therapy. However, it should not be offered if the patient is pregnant, and must be done with caution in the elderly.[4]

None of the major thyroid associations routinely recommend liothyronine.

Monitoring thyroid hormone replacement can be done using thyrotrophin as a tool for guidance, and titrating the dose based on this.

'Management can vary depending on the age of the individual affected. There are variations for pregnancy and childhood, as well as acceptance of conservative approaches in situations where more radical therapy may prove counter-productive.'

THYROID DISEASE IN OTHER SCENARIOS

Contrast media

The European Thyroid Association has issued new guidance on thyroid function abnormalities induced by iodine-based contrast media. Essentially, the recommendations provide advice on treatment and follow up, but dissuade from screening pre-scan, as it has no benefit. Treatment is only indicated when the thyroid dysfunction persists for a prolonged period, or in elderly patients with heart disease. There are no absolute monitoring recommendations, but thyroid dysfunction lasting for longer than two or three months after contrast administration will probably need treatment.[5]

Fertility

The latest European Thyroid Association guidelines suggest routine testing for mothers with reduced fertility, and aiming for an optimum level of thyrotrophin <2.5mIU/l. Information regarding the use of levothyroxine in patients undergoing artificial reproductive methods mainly focuses on aiming to improve success rates if patients have thyrotrophin >4.0mIU/l.[6]

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SPECIALIST PHARMACISTS IN ENDOCRINOLOGY AN EVOLVING ROLE

WRITTEN BY PHILIP NEWLAND-JONES, HANNAH SMURTHWAITE AND NABIL BOULOS

The role of the pharmacist has developed considerably over the past 20 years, with an increase in opportunities to work directly at the clinical 'coalface', as well as maintaining the backbone of medication procurement and dispensing in the NHS.

There are a considerable number of differing roles that pharmacists can undertake post-qualification, but the general direction is towards greater autonomous clinical practice. New regulations came into place in 2021 that stipulate that, from 2026, all pharmacists will be independent prescribers at qualification. Over the past 10 years, the development of pharmacists working clinically in secondary care and general practice settings has become far more structured and is now closely aligned to the physician model.

CAREER STRUCTURE

Pharmacists working in hospitals will spend two to three years post-qualification undertaking a postgraduate clinical diploma, with the development of a portfolio of evidence towards core advanced (generalist) competencies. If choosing a clinical specialist career path, such as endocrinology, they will then embark upon developing advanced competencies and have assessment against the advanced specialist framework, with the possibility of developing and mapping competencies against a consultant level framework (see Figure).

The title of 'Consultant Pharmacist' has far greater restriction than many other professions, with both the consultant pharmacist post itself having to be assessed and approved by the Royal Pharmaceutical Society, and a personal development portfolio being submitted for national assessment across four pillars of consultant practice: clinical practice, leadership, education and research.[1]

'The consultant pharmacist works as an autonomous clinical consultant with their own consultant clinic codes, responsible for organising, interpreting, prescribing and following up on endocrine investigations. All referrals are triaged by a medical consultant within the service.'

THE CASE FOR CHANGE

There has been a gradual increase in the number of pharmacists working nationally in endocrine services, which is expected to follow the same trajectory as secondary care diabetes services, with many more now employing a specialist pharmacist. The first consultant pharmacist nationally in endocrinology and diabetes was approved and appointed in 2017, with two further consultant pharmacist posts specifically in diabetes following in 2019 and 2021.

Endocrine services, now more than ever, need to increase service capacity and utilise the full multidisciplinary team (MDT) that is available. The mind initially drifts towards the obvious support a pharmacist could give to a service with frequent medication shortages, rare and high-cost medications, home care solutions and inpatient medication safety, but they can also be supported to develop as an autonomous clinical practitioner, as a permanent member of the clinical team.

CASE STUDY 1: CONSULTANT PHARMACIST

The consultant post was developed at University Hospital Southampton NHS Foundation Trust, a large tertiary endocrine centre. The post had a similar job plan to a medical consultant, with seven programmed activities (PAs) in direct clinical care and three PAs of supporting professional activities, which include regional and national diabetes and endocrine work. The post was created as 50:50 diabetes and endocrinology, with a mixture of inpatient and outpatient activity.

Regarding endocrinology, the consultant pharmacist works as an autonomous clinical consultant with their own consultant clinic codes, responsible for organising, interpreting, prescribing and following up on endocrine investigations. All referrals are triaged by a medical consultant within the service, and cases listed for the consultant pharmacist are a good mixture of general endocrinology. This releases consultant physician time to focus on more tertiary centre specialist activity, so increasing service capacity on a number of fronts. In addition, the consultant pharmacist assists specialist registrars with inpatient endocrine queries and oversight of outpatient clinics alongside consultant medical colleagues.

Working in a tertiary centre, the consultant pharmacist also supports the pituitary, adrenal, neuroendocrine and joint biochemistry MDTs, with a particular focus on complex case management. They have supported the development of joint working initiatives with oncology and neurology around the increase in monoclonal antibody-related endocrinopathies. Since January 2020, the consultant pharmacist has taken on the clinical director role within the diabetes and endocrine service, and undertakes all activities associated with this role, including consultant job planning. They have driven service development in areas such as andrology and male infertility, adrenal MDT pathways and non-diabetic hypoglycaemia.

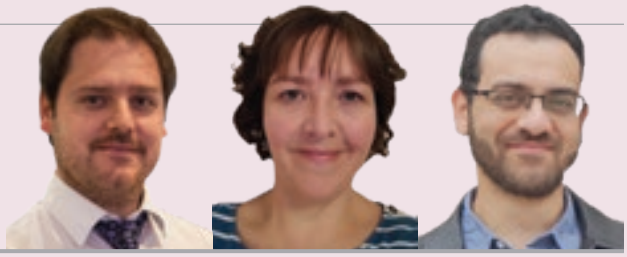
CASE STUDY 2: SPECIALIST ENDOCRINE PHARMACIST

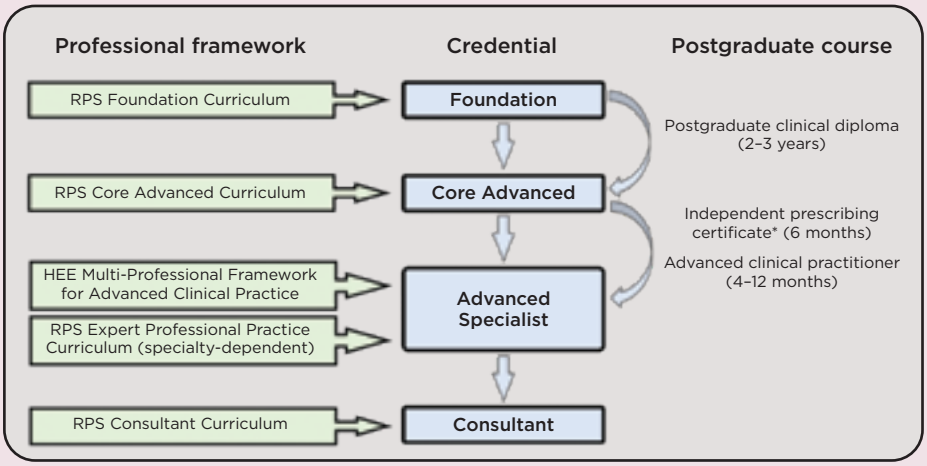
A specialist pharmacist for endocrinology can be trained to effectively self-manage significant cohorts of patients within specialist endocrine services. Case 2 describes a pharmacist appointed and embedded within a district general hospital where they now manage 25–30% of all endocrine outpatients within the service, focusing mainly on hyperthyroidism and adrenal incidentalomas.

Approximately 10% of patients are referred with adrenal incidentalomas, which are investigated using a standard protocol. However, multiple medications interfere with these investigations, particularly an aldosterone:renin ratio.[2] Switching to non-interfering medications whilst managing blood pressure can be difficult, but is routinely and confidently undertaken by experienced endocrine pharmacists. The pharmacist also manages this section of the adrenal MDT, deciding which patients should be discussed on each occasion, so that they are safely managed and have input from all the necessary specialists, including endocrinologists, radiologists and biochemists. Patients who are diagnosed with an active nodule can be transferred to consultant care as needed. and referred back to the pharmacist for ongoing monitoring, once a treatment plan is in place.

The endocrine pharmacist also supports the department through arranging the supply of hydrocortisone emergency kits for patients who have adrenal insufficiency, as well as education and training on sick day rules and when to use the kit.

From an inpatient perspective, admissions to hospital frequently result in missing or altered regular medications, such as long term steroids, and simple nasal sprays like desmopressin can be overlooked. Endocrine





Clinical pharmacist credentialing and professional progression pathway.[7] HEE, Health Education England; RPS, Royal Pharmaceutical Society. *New regulations came into place in 2021 stating that all pharmacists qualifying by 2026 will be independent prescribers on qualification.

pharmacists support the development of the whole pharmacy workforce to create a staff group that is refocused on medications safety within the area of endocrinology. They are also able to provide education to different staff groups across the Trust, to identify high risk and vital medications, and empower staff to detect and resolve any issues quickly, for the safety of patients.

CASE STUDY 3: PAEDIATRIC ENDOCRINE SPECIALIST PHARMACIST

The national clinical standards for paediatric endocrinology require a nominated paediatric pharmacist for lead specialist centres.[3] Despite this, the role of the paediatric endocrine pharmacist remains under-utilised nationally.

Children have unique pharmaceutical needs that pose two challenges to the clinician. First, there is genuine scarcity of an evidence base behind pharmacological management in children: hydrocortisone dosing in paediatric adrenal insufficiency and drugs for paediatric obesity are current hot topics and case examples. Secondly, children are a heterogenous group, with individual needs that often necessitate critical examination of the drug formulation being offered, its clinical appropriateness, practicality and cost-effectiveness.

In 2021, the pharmacist revived steroid medication review clinics, discussing medicine adherence, educating families on sick day rules, and training parents on emergency hydrocortisone injections. The aspect uniquely provided by the pharmacist was a review of hydrocortisone formulations: assessing the children's individual abilities and level of independence, discussing the available options with parents, and prescribing a different formulation as each child 'outgrows' their current one. With two recent national alerts on use of hydrocortisone formulations in children,[4,5] this task requires a practitioner experienced in both paediatrics and pharmaceutical care.

An example within a different setting is a pharmacist-led review of zoledronate day cases. The pharmacist is trained to assess the patient's history of fractures before each infusion, to prescribe zoledronic acid, pre-medication and discharge medicines, and then to carry out a bedside consultation to review the patient's management of bone disease through medication and diet. The new model allowed identification of patients on suboptimal vitamin D therapy, switching to more suitable calcium formulations to match the individual children's needs, and counselling on management of acute phase reaction post-infusion.

Another opportunity for pharmacists to provide support is in childhood obesity. In the UK, this has risen at an alarming rate, with one in four children now being obese at the time they leave primary school.[6] Given the early emergence of co-morbidities in this population, there is an urgent need for specialist practitioners in this field. In Southampton, the pharmacist works within the tier 3 service to use glucagon-like peptide-1 (GLP1) agonists for paediatric obesity. The role involves patient education on subcutaneous injection administration, pharmacist-led GLP1 review clinics, and independent prescribing for the service.

IN CONCLUSION

With the increase in 'advice and guidance' requests for endocrinology that has been seen over the past three years, service backlogs due to COVID-19, and a general increase in referrals into the specialty, greater senior clinician activity is needed in endocrine services. Nowadays, most endocrine services could not function without their specialist nursing team. However, considering the future needs of the endocrine workforce, we must consider utilising the full MDT, where pharmacists also evolve into being a core member of every endocrine team.

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MOLECULAR (FUNCTIONAL) IMAGING FOR PITUITARY ADENOMAS

WRITTEN BY OLYMPIA KOULOURI, WAIEL BASHARI AND MARK GURNELL

It was just after 6.30 p.m. when John Pickard (now Emeritus Professor of Neurosurgery at the University of Cambridge) leaned over and asked, "Surely there must be another way to locate these?"

We were sitting in the pituitary multidisciplinary team meeting, discussing the final case and peering hard at the screen, in the hope of discerning where the corticotroph adenoma was hiding. At the time, John was the lead pituitary surgeon in Cambridge, with extensive experience of transsphenoidal surgery. Perhaps just as importantly, he was Academic Head of Department and Director of the Wolfson Brain Imaging Centre, recognised for its pioneering work in traumatic brain injury and the use of positron emission tomography (PET) imaging.

And so began the journey to establish a molecular (functional) pituitary imaging service for UK patients, with two primary aims: (i) to improve the localisation of small microadenomas ('picoadenomas', to quote the distinguished pituitary neuroradiologist Jean-François Bonneville) and (ii) to more reliably discriminate residual or recurrent tumour from post-treatment remodelling after primary therapy.

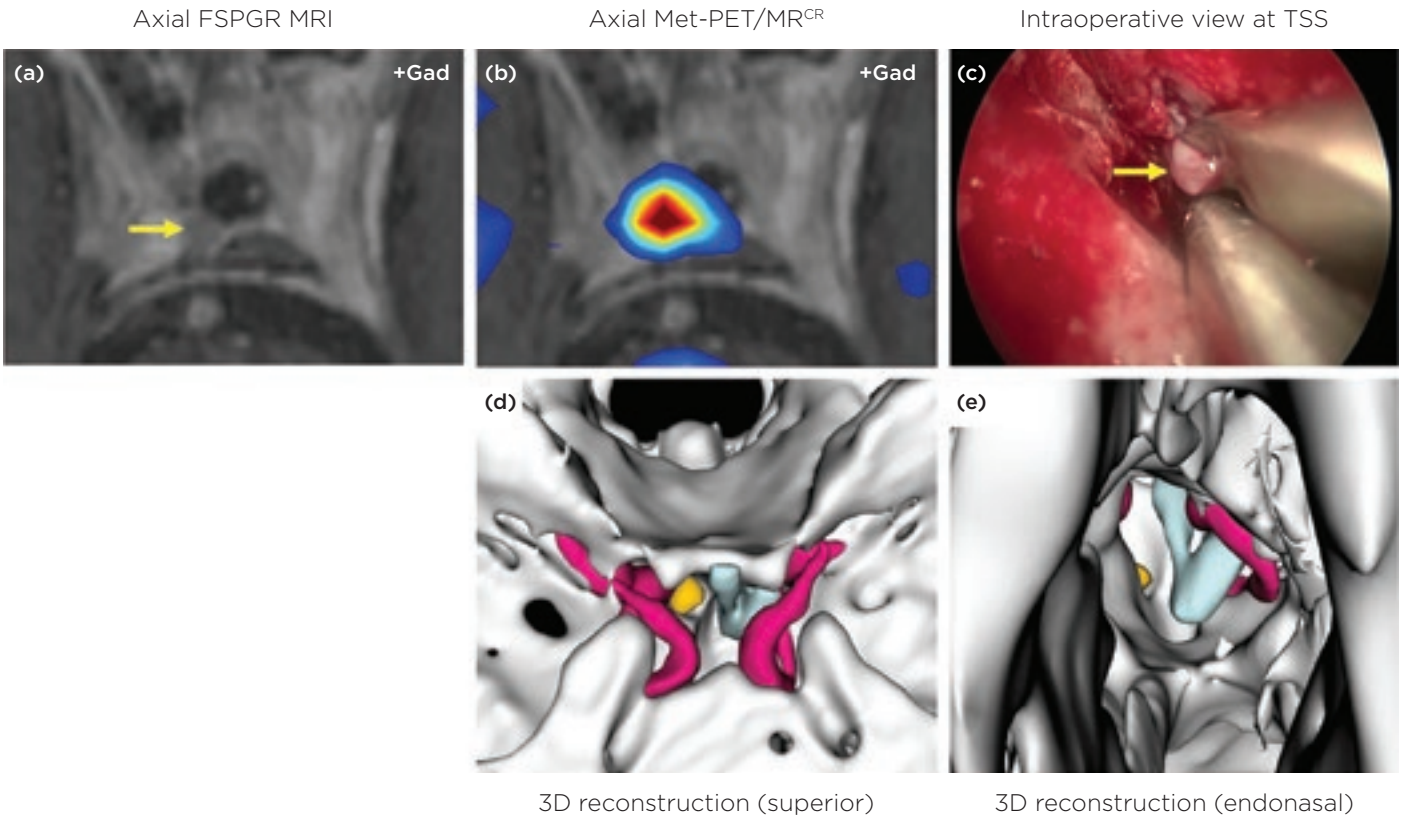
WHY WAS NO ONE USING PET?

In the initial phase of the project, the obvious question to ask was why nobody was using PET to localise pituitary adenomas. After all, endocrinologists are very comfortable with functional imaging in other disease areas, e.g. thyroid scintigraphy, parathyroid single photon emission computed tomography/computed tomography (SPECT/CT), ^{68}Ga-dotatate PET/CT.

On reviewing the literature, it became clear that several attempts had been made to find a suitable functional imaging strategy, but that each had encountered challenges.

First, which ligand should be preferred? ^{18}F-fluorodeoxyglucose (^{18}F-FDG), with its central role in clinical oncology, is readily available, but pituitary adenomas show very variable (even absent) tracer uptake. At the same time, avid ^{18}F-FDG uptake in adjacent brain tissue can confound scan interpretation. Other more selective ligands (e.g. those targeting

Met-PET/MR^{CR} in a patient with persistent acromegaly despite previous transsphenoidal surgery (TSS) on two occasions, radiotherapy (10 years earlier) and maximal somatostatin receptor ligand therapy. (a, b) Although no residual tumour could be visualised on standard coronal and sagittal images, Met-PET/MR^{CR} revealed an area of focal tracer uptake that could be appreciated on axial volumetric MRI (arrow). (c) At surgery, a small focus of residual tumour was resected (arrow) from the site identified on Met-PET/MR^{CR}. (d, e) 3D reconstructed images using PET, CT and MRI datasets, showing the position of the remnant adenoma (yellow) relative to the residual normal gland (turquoise) and intracavernous carotid artery (red). FSPGR, fast spoiled gradient recalled echo; Met-PET/MR^{CR}, ^{11}C-methionine PET co-registered with volumetric (FSPGR) MRI.



somatostatin or dopamine receptor expression) inevitably have more restricted usage, meaning that a panel of ligands would be required to image different pituitary adenoma subtypes.

'In the initial phase of the project, the obvious question to ask was why nobody was using PET to localise pituitary adenomas.'

Secondly, attempts to precisely localise sites of tracer uptake were hampered by the lack of spatial resolution of scintigraphy and SPECT/CT, and even PET/CT has limitations, given the modest structural information provided by CT when compared with magnetic resonance imaging (MRI) of the sella and parasellar regions.

IDENTIFYING ANOTHER METHOD

This prompted us to consider an alternative approach. A common property of most pituitary adenomas is peptide synthesis, even in clinically non-secretory tumours (as evidenced by immunohistochemical staining and *in vitro* cultures of resected tumours).[1] We therefore selected ^{11}C-methionine, which is taken up via the L-type amino acid transporter 1 (LAT1), as a 'universal' PET tracer (Met-PET). This was based on previous pilot studies that had confirmed uptake in different pituitary adenoma subtypes.

In parallel, colleagues in nuclear medicine, radiology and medical physics optimised algorithms to enable Met-PET/CT to be coregistered with volumetric (1-mm slice thickness) MRI to create hybrid images (Met-PET/MR^{CR}), that allow more accurate localisation of sites of tracer uptake through precise correlation with anatomical findings.

METHODOLOGY IN PRACTICE

So what is the experience to date with >700 scans performed in studies and clinical practice?

In acromegaly, Met-PET/MR^{CR} can help confirm suspected, or reveal unexpected, sites of residual disease following primary treatment (see Figure, page 14).[2] It can also provide key information about the degree of parasellar involvement, to permit repeat transsphenoidal surgery in patients previously considered to have unresectable lateral tumour extension.[3] In Cushing's disease, both *de novo* and recurrent corticotroph adenomas may be more readily visualised with Met-PET/MR^{CR} when MRI is indeterminate or negative.[4]

'Studies in the rarest pituitary adenoma subtype, thyrotroph adenomas, have also allowed development of novel approaches.'

Although microprolactinomas are traditionally managed with medical therapy, several groups have recently demonstrated comparable or superior outcomes following transsphenoidal surgery.[5] With increasing awareness that a significant proportion of patients experience intolerable side effects when treated with dopamine agonists (including impulse control disorder), the role of surgery is being re-evaluated.[6] In this setting, Met-PET/MR^{CR} has a potentially important role to play in patients with inconclusive MRI, because prolactinomas are ^{11}C-methionine-avid and therefore readily visualised. This can permit targeted selective adenomectomy without the need for more extensive exploration of the gland (Bashari *et al.* unpublished observations).

Studies in the rarest pituitary adenoma subtype, thyrotroph adenomas, have also allowed development of novel approaches. These include subtraction imaging, in which PET is performed before and after endocrine treatment to suppress tumour activity. This has particular value in microadenomas which are not clearly seen on MRI. Here, normalisation of thyroid function tests following somatostatin receptor ligand therapy correlates with extinction of the focus of ^{11}C-methionine uptake at the site of the tumour.[7]

'The advent of molecular imaging means that more patients can now be considered for definitive treatment (surgery or radiosurgery).'

OTHER IMPLICATIONS

Finally, combining data from multiple imaging modalities enables detailed 3D reconstructions of the sella and parasellar regions (Figure). This has the potential for incorporation into surgical planning and training and, at the same time, may facilitate patient understanding of a planned procedure, for example through 3D printing of individual patient models.[8] So, while MRI will remain the cornerstone of pituitary imaging in most patients, the advent of molecular imaging means that more patients can now be considered for definitive treatment (surgery or radiosurgery).[9]

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TECHNOLOGICAL ADVANCES IN NEUROENDOCRINE TUMOUR RESEARCH

WRITTEN BY KATE LINES

Neuroendocrine tumours (NETs) are tumours that occur in cells of the neuroendocrine system, i.e. a network of glands that produce hormones. These can include cells in the pancreas, lung and bowel. NETs are classified as rare. However, their prevalence is increasing, with approximately 4,000 people diagnosed in the UK each year.

NETs are graded based on their severity, from G1 to G3.[1] G1 NETs are the lowest grade and have the best prognosis. They are well differentiated and grow slowly. G2 NETs are an intermediate grade, with moderate differentiation and growth. G3 are the highest grade NET with the worst prognosis. They are poorly differentiated, and grow at a high rate. Diagnosis of the correct grade is important to determine the prognosis. Treatments also vary, based on the NET grade. They can include surgery, radiotherapy, chemotherapy or specific targeted treatments such as somatostatin analogues.[2]

Unsurprisingly, most of the recent research and developments have focused on improving diagnosis and treatment. These include the use of novel technologies to investigate the underlying biology, and the preclinical development of new therapies, as well as the evaluation of novel agents in clinical trials. In particular, studies have included identification of changes in the cellular environment (known as the microenvironment) of the NETs (see Figure, page 17),[3,4] not just the tumour cells themselves.

TECHNOLOGICAL PROGRESS

One of the most recent technological advances is the ability to assess gene expression changes at the single cell level, using single cell RNA sequencing (scRNA-Seq). This means that specific expression patterns can be observed in individual cells within a tumour, which can also be used to determine the different cell types present. This technology has already been used for multiple cancers but, more recently, it has been used to assess NETs, including those from the pancreas, lung and pituitary.

'Combining the single cell sequencing technology with the technology to isolate circulating tumour cells to look for malignant expression patterns could provide a particularly powerful diagnostic or prognostic tool.'

For example, a study in pancreatic NETs revealed the presence of immune cells and fibroblasts, as well as the NET cells, and identified a gene signature that could predict the malignant potential of the NET cells.[5] This study also showed that the microenvironment of the NET is very different to that surrounding metastatic tumour sites. This increased biological understanding can help in making treatment decisions, especially if you know that the NET and the metastatic tumour may respond differently to the treatments given.

The gene signature can also be used to aid diagnosis or as a biomarker. It was recently reported that the presence of circulating tumour cells in the blood of patients with a pancreatic NET could be used as biomarkers to categorise patients in clinical practice and trials.[6] This involves taking blood samples and isolating the tumour cells that are present within them.

Combining the single cell sequencing technology with the technology to isolate circulating tumour cells to look for malignant expression patterns could provide a particularly powerful diagnostic or prognostic tool.

LABORATORY MODELS

One of the biggest disadvantages of technologies like scRNA-Seq is the requirement for substantial amounts of patient material. Therefore, a challenge in NET research has always been to develop good laboratory models that accurately represent the tumours seen in patients. Cell lines are often used; however, they grow on 2D surfaces and exist as single cells, rather than as clusters of cells like the tumours in patients.

'Using technologies and models to investigate the whole tumour environment, rather than just the tumour cells themselves, has highlighted a number of other possible therapeutic targets.'

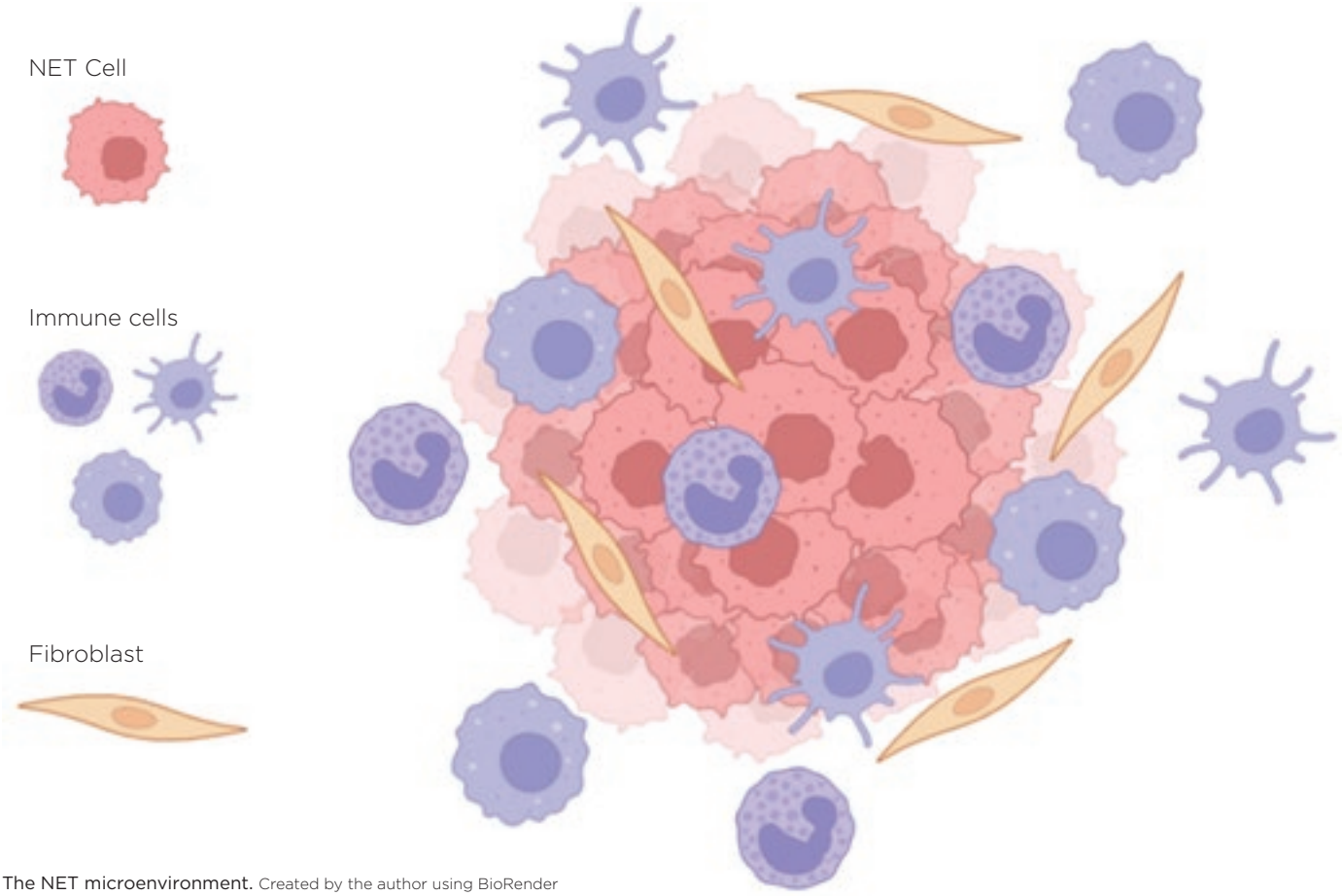
To overcome this, organoid models have been developed. These are 3D cell culture models that are established from patient tissues, and represent the tumours more closely than traditional cell lines, as they include many cell types that are present (including immune cells). A collection of NET organoid models was recently established.[7] This consists of lung, oesophagus, stomach, liver, biliary tract, pancreas, duodenum and colon organoids. All of these were comprehensively examined for genetic mutations, and gene expression changes. These have therefore provided a model to further examine the biology of NETs, and also have the potential to be used for the assessment of novel drugs.

THERAPEUTIC TARGETS

Using technologies and models like those mentioned above to investigate the whole tumour environment, rather than just the tumour cells themselves, has highlighted a number of other possible therapeutic targets.

One of particular interest recently is the immune system. Immunotherapy has shown great results in many cancer types, and has revolutionised cancer treatment. Clinical trials evaluating immunotherapy (consisting of antibodies targeting different immune-associated elements) have been undertaken in in NETS, but have had mixed results.[8]

Using immunotherapy alone appears to have a very limited effect, except in lung NETs where modest response rates have been reported with immune checkpoint inhibitors.[9] The use of two immunotherapy drugs in combination has, however, shown more promising results. For example, the



The NET microenvironment. Created by the author using BioRender

'There is still a long way to go to determine if these drugs will have a use in patients with a NET, but the continuing research into the NET immune environment … will help determine which patients should receive these drugs, and provide better methods to monitor their progress.'

combination of anti-CTLA-4 and anti-PD1 antibodies showed a response to the treatment in up to 44% of patients with high grade NETs.[10]

There is still a long way to go to determine if these drugs will have a use in patients with a NET, but the continuing research into the NET immune environment, as well as the development of better biomarkers to determine response rates, will help determine which patients should receive these drugs, and provide better methods to monitor their progress.

Overall, these are exciting times for NET research, and hopefully these scientific and medical advances will come together to improve patient care in the near future.

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UNDERSTANDING EXERKINES

WRITTEN BY CRAIG L DOIG

Exercise evokes profound changes in endocrine activity and whole body metabolism. The raised energetic demands require tissue-specific molecular exchanges to take place. Exercise-induced secretory factors or 'exerkines' are a mechanism of tissue cross-talk of growing popularity in research. This growth has seen them linked to an abundance of health benefits.

Physical activity is beneficial to the individual. This has been universally accepted for, give or take, a couple of thousand years. However, there is considerable mechanistic complexity underlying this most basic of statements. In particular, the high bar for understanding mechanisms of tissue-specific response to exercise has recently been further elevated. The identification of exercise-mediated release of secretory factors has been documented in most endocrine responsive tissues, including liver, muscle, adipose (brown and white), brain and bone. However, the functional roles of exerkines, their physiological impact and, in some cases, their very existence remain deeply contentious.

CELL–CELL ACTIONS

Recent studies have examined exerkines originating from a variety of skeletal muscle and adipose depots. Importantly, work in these tissues has identified white adipose changes in secretory profile in ageing humans. Though not in response to exercise, many of the prototypical secretory factors described as exercise-responsive were measured.[1] Not all showed significant changes during ageing, but profiles from serum showed a modest number of significant events (including a reduction in insulin). These data suggest that tissue-specific secretions (at least in the context of human ageing) may serve to direct local cell–cell actions as opposed to wider systemic roles. This does raise questions about the numerous physiological roles ascribed to exerkines from murine-focused studies.

'When understanding biological impact versus incidental observation, causal links for exerkines remain limited.'

Experimental work correlating adipokines released with diseased status are common. However, the array of adipose depots available for analysis makes conclusions difficult to reconcile. Extrapolation of these findings to physiological importance represents a considerable challenge. Nevertheless, recent work has made some progress. For example, the adipokine CTRP9 increases in children experiencing type 1 diabetes, and FGF21 increases in those living with type 2 diabetes. This implies that these adipokines may be relevant to disease status.[2] Moreover, the secretory factor resistin is hormonally regulated by vitamin D,[3] and has been shown to have a causal relationship with atrial fibrillation.[4] Again, these are not exercise-mediated actions, but hint at potential endocrine importance and indicate underpinning mechanisms.

EXERCISE-DEPENDENT METABOLITES

A recent, comprehensive study catalogued tissue-specific secretions over time. This revealed the acute sensitivity of organ responsiveness to exercise as well as its time-based nature.[5] It provided considerable insight into the complexities at play, identifying 600–900 exercise-dependent metabolites, dependent upon the tissue. Of note is the identification of 2-hydroxybutyrate as a time-dependent exerkine, given that it is already known as a marker of insulin resistance.[6]

'Does the type of exercise influence the secretory factors produced by any given tissue? Perhaps, but no one knows, and there is substantial room for new studies to generate new knowledge.'

When understanding biological impact versus incidental observation, causal links for exerkines remain limited. Resolution of temporal studies can be problematic, limited by the sample collection times and intervals between them. However, together with the increased understanding of extracellular vesicles, a concept arises for such modulators of organ–organ cross-talk to be exploited for therapeutic use. But, to achieve this, it still needs to be proved beyond doubt that extracellular vesicles serve a particular function, as reviewed by Darragh *et al.*[7]

In addition, does the type of exercise influence the secretory factors produced by any given tissue? Perhaps, but no one knows, and there is substantial room for new studies to generate new knowledge. A similar situation applies regarding the subject of cell heterogeneity. The technology to answer these questions is now more accessible. Methodology for sampling secreted factors is a crucial point, often overlooked. Consistency and accurate reporting of protocols for the measurement of secretory factors require greater standardisation.

FUTURE CHALLENGES

Many years after initial detection, we still are yet to understand how exercise-induced secretory factors interact with endocrine function and impact whole-body physiology (if at all). As awareness increases and technological barriers decrease, there is a growing need to catalogue and validate emergent secretory factors (including cardiokines, osteokines and hepatokines).

All in all, we do understand that organs exhibit an element of cross-talk in response to physical exertion. The secreted elements termed exerkines may contribute to the beneficial impacts of exercise, though this remains to be demonstrated in humans. Moreover, emerging studies show the range of secretory factors released in response to exercise are probably tissue-specific and certainly circadian-influenced. Deconvoluting such responses represents a considerable scientific challenge.

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AN INTERVIEW WITH... CYNTHIA ANDONIADOU

Cynthia Andoniadou is Reader in Stem Cell Biology and Associate Dean for Postgraduate Research at King's College London, where she established her research group in 2013. She is also the recipient of the Society for Endocrinology's 2022 Starling Medal, which honours an emerging outstanding scientist whose work has contributed to exceptional advances in endocrinology. Here, she talks about her life in endocrinology to Kim Jonas.

Kim: Can you describe your central area of research?

Cynthia: Yes, my main interest is endocrine stem cells. We have been focusing on pituitary stem cells and recently expanding to the adrenal medulla. The central questions that underlie the research aim to understand what these cells do throughout life, and how do they do it. We want to know how they contribute to and regulate endocrine function. Are they there just as a supply of new cells, in case of the requirement for organ plasticity (for example if there is physiological challenge), or do they have additional roles?

So, we have started the work of identifying and characterising the stem cells in an organ, to try to understand their behaviour, particularly during homeostasis, physiological challenge and disease. In terms of their cell biology, the part that I'm most interested in is signalling: in particular, paracrine signalling emerging from the stem cells and influencing the other cells in the environment. The research that we have published in the last few years has revealed that stem cells secrete ligands into their environment, which modify the behaviour of other cells.

An example in the pituitary gland is WNT signalling, and how WNT ligands promote the proliferation of more committed progenitors. This is essential for growth of the gland; without this paracrine stem cell action, the gland doesn't expand, which, in mice, leads to hypopituitarism.

There are multiple aspects of the contribution of stem cells that haven't been explored, for example, during the adaptation of the gland or during disease. Our unpublished research is hinting that stem cells can influence more than just proliferation, so they might be involved in multiple aspects of pituitary gland function.

K: How did you begin to explore the role of stem cells through endocrine research? What led you to that path of stem cell discovery?

C: My research went full circle. I did my undergraduate degree in genetics and microbiology. Very soon into the course, I realised I hated microbiology, so I focused more on genetics. I did a PhD at the National Institute for Medical Research, London, in the Developmental Genetics Division, working on stem cells of the central nervous system and, specifically, the role of SOX2, which marks many epithelial stem cells.

My work was mostly based *in vitro*, so, for my postdoc, I wanted to go back into the organism and focus more on developmental biology. I joined Juan Pedro Martinez-Barbera's lab at the UCL Institute of Child Health, London, and started my postdoc research on anterior forebrain development. It was a fantastic training opportunity for me. A large part of it involved manipulating genes and signalling pathways using genetically altered mouse models.

I was using a specific Cre-driver to activate the WNT signalling pathway in the forebrain, and the Cre recombinase was expressed not only in the forebrain but also the pituitary gland. I was disappointed when there was no phenotype in the forebrain. However, when we looked at the pituitary gland, we realised the mutation led to pituitary tumours. Looking at that phenotype in more detail revealed that there was involvement of stem cells, which got me back into studying stem cells, this time in the pituitary gland. So that was exciting for me, because I really do love stem cells.

K: Can you tell us about the multi-omics approaches that you've been using recently, why you've taken that direction and how it's benefited your research?

C: We started off doing bulk RNA sequencing and purifying populations in the lab to compare stem cells with non-stem cells, and realised that this approach can give very misleading information. It is fine if you only have pure cell populations to compare, but all endocrine cells were present in one sample, and the resolution of the technique was not sufficient to draw certain conclusions.

When single cell technologies started emerging, it presented a fantastic opportunity to see what the relationships are between cells. Specifically, we wanted to study the communication between cells and to know exactly which genes stem cells express and, therefore, the proteins they potentially secrete, which cells might be perceiving as signals. This is all key to much of the research that we are doing.

We knew from immunofluorescent staining and cell culture experiments that not all stem cells behave in the same way or express identical markers. Therefore, we wanted to know what the degree of heterogeneity was amongst this population, and had the genetic tools to purify stem cells and characterise them better. We then started using single cell sequencing techniques to analyse stem cells of different genetically modified mutants, for example, ones with impaired secretion.

Our work has led to us teaming up with wonderful collaborators, Stuart Sealfon and Frédérique Ruf-Zamojski, from the Icahn School of Medicine at Mount Sinai (New York, USA), who are experts in multi-omics techniques. Together, we analysed the human pituitary stem cell compartment and found that this is very similar to that of the mouse, which our collaborators had characterised by multi-ome, bringing confidence in the relevance of much of our stem cell work in mice.

Analysing human samples from frozen, post-mortem, pituitaries differs from the single cell RNA-seq approaches that we previously used, as the method employed used isolated single nuclei. As well as RNA-seq, this allows us to perform ATAC-seq, a method used to determine to what degree chromatin is accessible across the genome. This provides a valuable insight into how cells are regulated, gaining the label 'multi-ome'. During ATAC-seq, sequencing adapters are inserted into the accessible DNA regions, which

can then undergo high throughput sequencing. ATAC-seq does not require prior knowledge of genomic elements (such as promoters and enhancers). It can act as a powerful tool to help determine normal mechanisms of gene regulation and identify how these might go wrong, especially when combined with RNA-seq assessing gene expression.

This allows us to interrogate and understand the networks that are controlling cell fate, and capture changes that might happen during ageing or with disease. As this technique can use frozen tissue, it opens up the possibility of using archived tissue samples. It was crucial to first start with a multi-ome reference of normal glands, at different ages and across sexes.

K: How do you think the developments in -omics will open up the fields for us as endocrinologists, with the prospects for future discoveries that they may bring?

C: It is important to mention that the amount of data generated from just a single piece of tissue is enormous. It's enough to sustain multiple labs with multiple projects until the end of their careers!

At this point, I don't foresee it being used for diagnosis (famous last words). It's unlikely to replace current techniques that assess which cells are normal or what mutations might be present, mostly because of the cost and time it takes for data to be analysed. However, as discovery research, it can lead to a much deeper understanding of disease pathogenesis, and eventually may be of great value to personalised medicine.

At these early stages, we might just have to sequence or multi-ome everything, to gain global information on baseline cell states. As a next phase, disease cell states can help us identify and design new drug targets, and select appropriate treatments that target cells selectively (for example, only cells identified as 'tumourigenic culprits' in a tumour). Eventually, having extended multi-ome libraries of diseased tissues, with associated clinical data or outcomes (such as response to specific treatments), will be a worthwhile investment. It will be critical to retain the data in open access format for professionals.

K: With every new technique comes limitations. What are the considerations when using these new approaches?

C: Tissue integrity is crucial. This can be difficult if you are working with human samples that are collected via post-mortem or partially processed by pathology labs. With mouse samples, which we primarily work on, we can control the tissue handling and processing more.

I offer a word of caution on data processing. Anyone can pay and outsource the running of a multi-omics experiment if they have access to the samples, but doing the analysis is the particularly tricky part. You need to have access to trained computational biologists who understand the data and have the biological knowledge to ask the right questions in the right way. So, we need to have common language and understanding with computational biologists.

As a computationally challenged biologist, I can't understand code that I am shown and can only advise how queries are approached, but I am lucky that my team are proficient in both! New pipelines for data analysis algorithms are emerging all the time, and something that we are lucky to have is a worldwide network of collaborators, who support one another during analysis, and exchange code if required. If we have a problem then we can put that forward, discuss it all together, and come up with solutions. Analysis is going to be a little bit slower until the necessary code is developed to extract everything we need, but, once this is all in place, the analyses will be far more user-friendly.

Cynthia and her team, clockwise from top: Val Yianni, Thea Willis, Emily Lodge, Alice Santambrogio, Cynthia, Yasmine Kemkem (not present: Carlos Abascal Sherwell Sanchez).

A final limitation is space. These datasets are enormous, and not all institutions have yet caught up with the server space required for the datasets generated by their investigators. This will remain a major consideration in the future, when there will hopefully be concerted efforts to pool data from multiple studies, and curate them all in a user-friendly format, accessible online.

K: I wanted to end by congratulating you for being awarded the 2022 Starling Medal!

C: Thank you! I am so grateful to the Society for Endocrinology and, especially, as a basic scientist, as I feel truly welcomed into the endocrine community. As a lab, and in the stem cell field, I think we are gaining momentum at present, which is a really nice place to be.

The Starling Medal represents recognition of the cumulative work of everybody who has shaped the research. There are many people who have contributed to this, including all the researchers who have been part of my lab, our clinical, translational and basic collaborators, and the scientists who trained me along the way.

When it comes to my lecture, I will try my best to include contributions from as many people as possible, since it feels strange to receive a medal bearing only your name, when a hundred names are also behind the work.

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We need many voices represented in the Society's leadership, on our Council and Committees, so we can evolve and adapt to support endocrinology into the future. This especially important post-pandemic, as our members are facing new and different challenges that the Society needs to better understand.

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Giles Yeo

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HELP CHAMPION UNDERSTANDING OF HORMONES AND THEIR HEALTH IMPACT

Spread the word about our website You and Your Hormones as an educational resource to your students, patients, families, friends and even your kids' schools. This valuable resource achieved an Association for Science Education (ASE) Green Tick last year: the result of updates by our Public Engagement Committee, as part of the Society's mission to promote accurate knowledge. Now more easily searchable, mobile-friendly and image-driven, it should be the first port of call for authoritative, expert and engaging information about hormones. Visit **www.yourhormones.info**.

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It includes content created by Society members, and resources from their institutions or from external societies and organisations, including patient support groups. Overseen by our Clinical Committee, this live depository will continue to grow with your help, and support our members to deliver the best possible patient care.

Current sections include Patient Safety, Research, Patient Support Groups, recommendations from Defining the Future of Endocrinology and general resources. Future developments will enable you to comment on individual resources, rate them and upload your own resources directly.

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Strengthening representation **ACROSS YOUR SOCIETY**

In 2020, the Society for Endocrinology convened a member working group, led by Professor Karen Chapman, to conduct a review of its governance. This included the structure of our Council and Committees and other decision-making groups, the breadth of expertise represented and the underpinning processes.

The group concluded that, although the Society was well-run and effective, it could, and should, do more to embed equality, diversity and inclusion practices across its governance, to enable it to best fulfil its mission.

The review identified four main themes for development:

(a) better representation of the **diversity of the Society's membership** within the governance structure, including under-represented groups such as clinicians working at district general hospitals, nurses and early career members

(b) more **clarity and transparency over election processes** to foster better member engagement, which should translate into better diversity within the governance structure

(c) greater focus on recruiting and supporting **the development of early career endocrinologists**, utilising early career members' experiences to inform decision making

(d) increased emphasis on **education and training** within the governance structure, which should support the above aims.

Society members were consulted on the group's recommendations before they were discussed by Council in September 2021. Of the 92 individual recommendations, 47 were approved as written, and the remainder will be reconsidered in the spirit with which they were put forward.

The main activities now underway to address the recommendations are:

- setting up a new member-led working group to consider **equality, diversity and inclusion**
- increasing clarity and transparency around all governance processes, including clear **role descriptions with statements of desirable skills**
- replacing nominations with **an application-based election process**, to increase inclusivity and foster better member engagement, particularly from under-represented groups
- improving clarity and transparency for all **medal, prize and grant processes**
- reviewing progress and setting **a strategy for education and training** with members from across all Society Committees at twice yearly meetings.

You can read the full Governance Review report at **www.endocrinology.org/governance**

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Your chance to **REWARD EXCELLENCE IN ENDOCRINOLOGY**

Our Medals and Awards aim to recognise and celebrate individuals who advance our discipline through scientific, clinical or educational achievements. Medallists and Awardees present lectures at our SfE BES conference, where you can learn more about their work and achievements. Now is your chance to help us identify the recipients of these honours in the coming year.

MEDALS

Society Medals are awarded to world-leading scientists and clinicians who have carried out landmark work over their lifetime, which continues to inform research and best practice in the field.

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Awarded to a member of the scientific community in recognition of outstanding studies which have changed our understanding of endocrinology in a fundamental way. The Dale Medal is the highest accolade bestowed by the Society.

JUBILEE MEDAL

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Joint Position Statement on Best Practice Recommendations for the Care of Women Experiencing the Menopause

BY THE BRITISH MENOPAUSE SOCIETY, ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS AND SOCIETY FOR ENDOCRINOLOGY

Best practice recommendations for healthcare professionals providing help and support to women experiencing the menopause have been issued in a joint position statement, with the Society's involvement led by our Clinical Committee. The statement was compiled in response to growing concerns around hormone replacement therapy (HRT) shortages and misinformation in the mainstream media.

POSITION STATEMENT

The British Menopause Society, Royal College of Obstetricians and Gynaecologists and the Society for Endocrinology have produced this joint position statement to provide guidance to healthcare practitioners who offer care to women experiencing the menopause.

The menopause transition can have a significant impact on many women, with more than 75% experiencing menopausal symptoms and a quarter describing their symptoms as severe. A third experience long term symptoms, which may last as much as seven years or longer.

The aim of this position statement is to provide evidence-based recommendations on best practice in line with current national and international guidelines and recommendations.

Our recommendations are as follows:

- All women should be able to access advice on how they can optimise their menopause transition and the years beyond. There should be an individualised approach in assessing women experiencing the menopause, with particular reference to lifestyle advice, diet modification as well as discussion of the role of interventions including HRT.
- Women should be advised that implementing or maintaining a healthy lifestyle can improve menopause symptoms. A healthy diet (one low in saturated fat and salt and rich in calcium and vitamin D), stopping smoking, reducing alcohol intake and including regular exercise can be beneficial. Reducing caffeine intake may also improve symptoms.
- Alternative therapies, including cognitive behavioural therapy, may also improve hot flushes, night sweats and other menopausal symptoms and can be considered in women who do not wish to take HRT or have contraindications to taking HRT.
- The decision whether to take HRT, the dose and duration of its use should be made on an individualised basis after discussing the benefits and risks with each patient. This should be considered in the context of the overall benefits obtained from using HRT including symptom control and improving quality of life as well as considering the bone and cardiovascular benefits associated with HRT use. Discussions with women should also cover aspects such as when to consider stopping HRT and how this can be done (by gradually reducing the dose of HRT). No arbitrary limits should be set on age or duration of HRT intake.
- HRT, compared with placebo, has been consistently shown to improve menopausal symptoms and it remains the most effective treatment that is also associated with significant improvement in overall quality of life.
- In addition, HRT has been shown to have an effective role in the prevention and treatment of osteoporosis. Bisphosphonates are considered as first-line options for most patients with postmenopausal osteoporosis due to their broad spectrum of anti-fracture efficacy. HRT may be considered as an additional alternative option, particularly in younger postmenopausal women with menopausal symptoms who are at increased risk of fractures.
- HRT is considered as first-line intervention for the prevention and treatment of osteoporosis in women with premature ovarian insufficiency (POI) and early menopause (40–45 years old).
- Evidence from Cochrane database analysis suggests that HRT started before the age of 60 or within 10 years of the menopause may result in reduction in atherosclerosis progression, coronary heart disease and may lower cardiovascular and all-cause mortality.
- Current evidence suggests that oestrogen-alone HRT is associated with a lower risk of breast cancer than combined HRT. Breast cancer risk is duration dependent and may vary with the type of progestogen used. The risk of breast cancer should be considered in the context of the overall benefits and risks associated with HRT intake.
- Women with POI and early menopause (40–45 years old) should be advised that HRT is unlikely to increase risk of breast cancer in younger menopausal women under the age of 50. The meta-analysis by the Collaborative Group on Hormonal Factors in Breast Cancer in 2019 reported that the use of HRT in postmenopausal women younger than 50 increases the risk of breast cancer diagnosis which contradicts previous evidence and advice to date. However, the control group of age-matched postmenopausal women was inappropriate

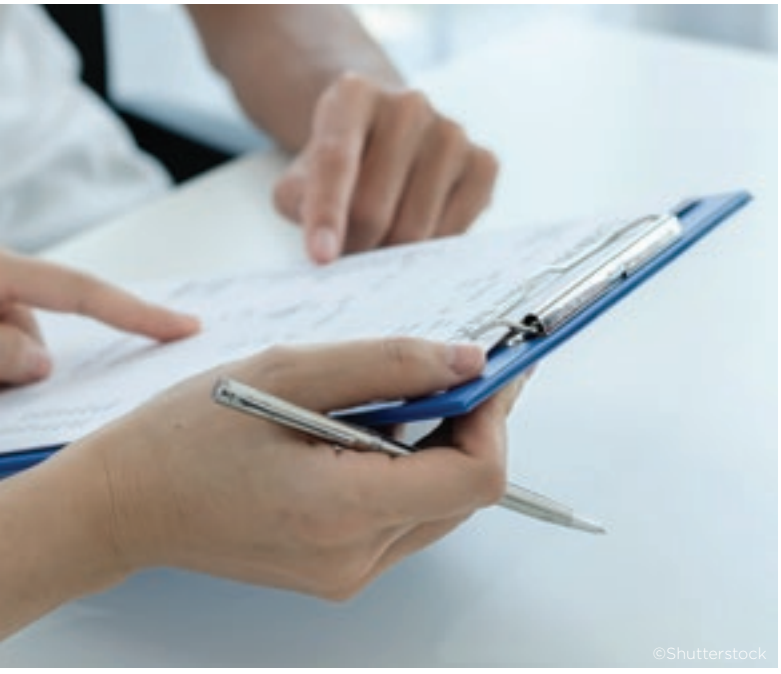
as an early menopause reduces breast cancer risk. Current recommendations are that the risk of breast cancer in relation to the years of HRT exposure in women with POI/early menopause should be counted from the average age of natural menopause (from the age 50 years).

- A history of breast cancer should be considered a contraindication to systemic HRT. The risk of breast cancer recurrence with HRT is higher in women with oestrogen receptor-positive cancer, but women with oestrogen receptor-negative breast cancer are also considered to have an increased risk of recurrence with HRT. HRT may, in exceptional cases, be offered to women with breast cancer with severe menopausal symptoms if lifestyle modifications and non hormonal treatment options are not effective. This should be done after discussion with the woman, her menopause specialist and her breast/oncology team.

- Women should be reassured that HRT is unlikely to increase the risk of dementia or to have a detrimental effect on cognitive function in women initiating HRT before the age of 65. However, HRT should not be initiated for the purpose of reducing the risk of dementia in women experiencing the menopause. National as well as international recommendations do not support the use of HRT for the primary or secondary prevention of dementia.

- Transdermal administration of oestradiol is unlikely to increase the risk of venous thrombosis or stroke above that in non-users and is associated with a lower risk compared with oral administration of oestradiol. The transdermal route should therefore be considered as the first choice route of oestradiol administration in women with related risk factors.

- For most women, initiating HRT has a favourable benefit/risk profile. However, HRT should not be used without a clear indication and should not be used for the sole purpose of disease prevention. Menopause is a life stage and does not represent a deficiency state. Menopause should not be compared with conditions such as hypothyroidism or type 1 diabetes mellitus.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- Women with a uterus require progestogen (administered for 12–14 days a cycle in a sequential regimen in perimenopausal women and daily in a continuous combined regimen in menopausal women) to minimise the risk of endometrial hyperplasia and endometrial cancer associated with unopposed oestrogen exposure. Sequential regimens can be delivered through oral and transdermal patch preparations while continuous combined regimens can be delivered through oral and transdermal patch preparations or through a 52 mg levonorgestrel releasing intrauterine system.

- The dose of the progestogen should be proportionate to the dose of oestrogen. Women who require higher doses of oestrogen intake should consider having their progestogen dose increased to ensure adequate endometrial protection.

- Low dose and ultra-low dose vaginal oestrogen preparations can be taken by perimenopausal and menopausal women experiencing genitourinary symptoms and continued for as long as required. All vaginal oestrogen preparations have been shown to be effective in this context and there is no requirement to combine vaginal oestrogens with systemic progestogen treatment for endometrial protection, as low dose and ultra-low dose vaginal oestrogen preparations do not result in significant systemic absorption or endometrial hyperplasia.

- Testosterone supplementation can be considered in women with low sexual desire if systemic HRT resulting in adequate levels of oestrogen with or without progestogen has not been effective.

- There is lack of evidence to support testosterone supplementation for the purpose of prevention or improving cognitive function, musculoskeletal health, improving bone density or fracture prevention. Testosterone supplementations should therefore not be offered for these indications.

- Women with POI and early menopause (40–45 years old) should be advised to take hormone replacement at least until the average age of the menopause.

- HRT should not be recommended for the primary or secondary prevention of chronic disease in women experiencing the menopause in keeping with national and international guidelines.

- The use of compounded bioidentical hormone replacement therapies is not recommended given the issues related to their purity, potency and safety. The potential benefits of bioidentical hormone therapy can be achieved using conventionally licensed products available through NHS prescribing without having to resort to compounded varieties from specialist pharmacies.

CONCLUSION

Women experience the menopause in different ways. Whilst some women experience minimal or no symptoms going through the menopause, many women experience menopausal symptoms that can significantly impact their quality of life. There should be an individualised approach in assessing women going through the menopause, with particular reference to lifestyle advice, diet modification as well as discussing the role of interventions including HRT. Women should be aware that help and support are available to them and should consult their GP for advice.

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DAVID TENNENT BAIRD (1935–2022)

David Baird, one of the country's most eminent figures in the field of obstetrics, gynaecology and reproductive biology, died in February 2022 at the age of 86. Reflections on his life and contributions shared by former colleagues, associates, trainees and patients testify to an unparalleled reputation as a research leader, teacher and caring clinician. He remained a life-long mentor, friend and source of wise counsel to those who were privileged to know and work with him. He was a passionate advocate for the rights and health of women and for women in medicine.

David Baird was born in Glasgow in 1935 into a medical family. His father, Sir Dugald Baird, at the time a senior lecturer at the University of Glasgow, was later appointed Regius Professor of Obstetrics and Gynaecology at the University of Aberdeen. David attended Aberdeen Grammar School and the University of Aberdeen, before taking the Natural Sciences Tripos at Trinity College, Cambridge, and proceeding to clinical studies at the University of Edinburgh, graduating in medicine in 1959. His early clinical training was in endocrinology, and obstetrics and gynaecology, in Edinburgh and London. He was a Fellow of the Royal College of Obstetricians and Gynaecologists (RCOG) and of the Royal College of Physicians of Edinburgh (RCP Edin).

David's many internationally recognised scientific and clinical contributions have had a huge impact on women's healthcare and on the careers of colleagues in his discipline worldwide. His past trainees and collaborators have spread his influence in every continent. David's training enabled him to bridge the gap between basic science and clinical research, and his clinical experience allowed him to identify important problems for research and to detect the impracticability of some scientific suggestions. His vision of the added value of scientists working alongside clinicians, close to their patients, underpinned the establishment of the University of Edinburgh Centre for Reproductive Biology in 1972, creating a model that was to be emulated in many countries.

David embraced the developing science of reproductive endocrinology in the 1960s when, appointed to a prestigious research fellowship at the Worcester Foundation for Experimental Biology (MA, USA), he began his life-long interest in experimental reproductive biology and the use of animal models to answer crucial research questions. He played a leading role in the development of the first chemical assay for the measurement of the sex hormones oestradiol and oestrone in blood. Working with Tait at the Worcester Foundation, he explored the concepts of steroid prehormones, which have since been widely applied in other systems. Further seminal work addressed hitherto-unrecognised roles for prostaglandins in reproduction. He demonstrated the remarkable biological phenomenon whereby prostaglandin F2α from the uterus travels against the bloodstream to reach the corpus luteum in the ovary, and bring about its demise (luteolysis) at the end of each ovarian cycle. This and other discoveries led to new and valuable applications, both clinically and in livestock reproduction.

David returned to Edinburgh in 1968 as lecturer in the University Department of Obstetrics and Gynaecology and was promoted to senior lecturer in 1970, along with his appointment as consultant obstetrician and gynaecologist at the Simpson Memorial Maternity Pavilion and the Royal Infirmary of Edinburgh. In 1972, with Roger Short, he established the MRC Reproductive Biology Unit, where he was Deputy Director until 1977, when he was appointed Professor of Obstetrics and Gynaecology at the University of Edinburgh. David felt that the responsibilities of a clinical professor inevitably restricted his research activities, and it was always his intention to limit his tenure of the Chair of Obstetrics and Gynaecology. From 1985 until his retirement in 2000 he held the position of MRC Clinical Research Professor of Reproductive Endocrinology, the final move of his career.

'He was passionate about the globally important issues of fertility control, and pursued the widening of options for contraception and safe medical abortion, pioneering the use of prostaglandins and then, crucially, progesterone receptor antagonists.'

David was the most eminent British gynaecological endocrinologist of his generation. He established many international collaborations, particularly with reproductive scientists in Australia, developed during a sabbatical there. He wrote over 400 peer-reviewed scientific publications and was editor of several books on reproduction. He pursued his belief of the need for improved understanding of human reproductive biology and its translation to benefit individual patients. And he engaged the Government, the medical profession and the public in the ethical and scientific debates surrounding these fundamental scientific advances.

His further original research contributions included the elucidation of the basic biological mechanisms in the control and function of the human gonads and the gametes they produce. He applied his world-leading expertise and knowledge to the early development of assisted reproduction techniques, including ovulation induction and *in vitro* fertilisation, and he made important contributions to the understanding of the regulation of ovarian follicle development and selection, and implantation and early pregnancy development. His findings continue to be relevant to clinical practice today.

His pioneering development of a unique method of studying the ovary in the sheep, by transplanting it to an accessible site on the animal's neck, led to major advances in understanding the regulation and function of the ovary. Using the sheep, he established cryopreservation of ovarian tissue and demonstrated the retention of its gamete- and hormone-producing capacities. This pivotal contribution to the field of female fertility preservation has transformed the lives of young cancer survivors treated with radiotherapy and/or chemotherapy.

He was passionate about the globally important issues of fertility control, and pursued the widening of options for contraception and safe medical abortion, pioneering the use of prostaglandins and then, crucially, progesterone receptor antagonists. He was extremely proud of his role in the development of medical abortion, which has saved many lives around the world. In 1995, he led the establishment at the University of Edinburgh of the Contraceptive Development Network, with funding from the MRC and the Overseas Development Administration, and its successor the Department for International Development, to harness international collaborations in Africa and China, in order to deliver novel approaches to contraception, including hormonal methods in men.

David's many clinical and research achievements received widespread recognition. He was awarded the Marshall Medal of the Society for the Study of Fertility, the Dale Medal of the Society for Endocrinology, and the Eardley Holland Gold Medal of the Royal College of Obstetricians and Gynaecologists. He was appointed Fellow of the Royal Society of Edinburgh, and awarded a CBE in 2000 for services to obstetrics and gynaecology.

David's input was extremely important to all those who worked for him. He inspired hard work and, above all, he gave encouragement when things got difficult. He had the gift of facilitating a way through a seemingly insurmountable problem. His advice continued to be highly valued throughout our careers.

David had a life-long love of Scottish mountains and the great outdoors, and he and his wife Anna always offered the warmest of welcomes at their cottage on the north shore of Loch Tummel. He will be greatly missed by many, and those who knew him will hold treasured memories of an exceptional man.

Our thoughts and sincere condolences are with David's family.

HILARY CRITCHLEY, IAIN CAMERON, ANDREW CALDER, MARY ANN LUMSDEN, RICHARD ANDERSON AND ALLAN TEMPLETON

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